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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/523,809	03/13/2000	Michael P. Murphy	56001/02822	6553

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EXAMINER

KAUSHAL, SUMESH

ART UNIT PAPER NUMBER

1633

DATE MAILED: 03/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/523,809

Applicant(s)

MURPHY ET AL.

Examiner

Sumesh Kaushal Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 December 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 31-71 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 31-71 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's remarks and declaration filed on 12/20/05 has been acknowledged.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is 571-273-8300.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 31-71 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the same reasons of record as set forth in the office action mailed on 06/16/05.

Nature of Invention:

Invention relates to an artificial skin construct.

Breadth of Claims and Guidance Provided in the Specification

The scope of instant claims encompasses a cultured skin construct having at least two layers, comprising: a) a first layer of cultured dermal fibroblast cells which produce a layer of extracellular matrix in the absence of exogenous matrix components during the culturing conditions (*any and all: growth factor and culture conditions not defined i.e. the support on which the cell are cultured*); and (b) a second layer of keratinocyte cells disposed on the first layer to form an epidermal cell layer, wherein the epidermal cell layer is multilayered, stratified, differentiated and exhibits a basal layer, suprabasal layer, a granular layer and a

stratum corneum; and wherein the bilayered cultured skin construct has a basement membrane present at the junction of the first and second layers *(wherein the keratinocyte cells makes an epidermal layer (as claimed) under any and all culture conditions: i.e. growth factors and culture conditions)*.

The scope of instant claims encompasses further encompasses a cultured skin construct having at least two layers, comprising: a) a first layer of cultured dermal fibroblast cells which produce a layer of extracellular matrix in the absence of exogenous matrix components during the culturing conditions *(any and all: growth factor and culture conditions not defined, i.e. the support on which the cell are cultured)*; and (b) a second layer of keratinocyte cells disposed on the first layer to form an epidermal cell layer *wherein the keratinocyte cells makes an epidermal layer (as claimed) under any and all culture conditions: i.e. growth factors and culture conditions)*.

The scope of invention further encompasses a cultured skin construct having at least three layers, comprising: a) a first layer of cultured dermal fibroblast cells which produce a layer of extracellular matrix in the absence of exogenous matrix components during the culturing conditions *(any and all: growth factor and culture conditions not defined)*; and (b) a second layer of keratinocyte cells disposed on the first layer to form an epidermal cell layer *(wherein the keratinocyte cells makes an epidermal layer (as claimed) under any and all culture conditions: i.e. growth factors and culture conditions)* c) and a third layer of cells deposited on the second layer.

In addition the scope of invention as claimed encompasses method of producing and using the above mentioned skin construct for transplantation or implantation into a patient.

Even though the specification teaches optimization of culture conditions for human fibroblasts to produce a layer of extracellular matrix in the absence of exogenous matrix components (see spec. Examples 1, 3 and 15), the specification fails to disclose what are the culturing conditions i.e. culture media contents, growth factors, culture environment that leads to the synthesis of (i)

type I and type III collagen, (ii) decorin, (iii) fibronectin, (iv) tenascin, and, (v) glycosaminoglycans. Specifically, the specification fails to disclose a culturing condition (culture media contents, growth factors, culture environment) in which the fibroblast cells when cultured produce type I and type III collagens (as claimed) and tenascin. The specification fails to identify type I and type III collagens (as claimed) and tenascin in the extracellular matrix secreted by cultured fibroblasts. In addition the specification fails to disclose that fibroblast cells derived from tissues selected from tendon, lung, cartilage, urethra, corneal stroma, oral mucosa, umbilical cord, and intestine are capable of synthesizing extracellular components (as claimed) under any and all culture conditions. Regarding formation of an epidermal layer the specification only disclosed the use of a specific culture conditions, which comprises culturing the seeded keratinocytes in an epidermalization medium followed by culturing of the skin construct under submerged conditions (air-liquid interface) in a culture media that is different from the epidermalization medium (Spec. page 46, example-16). The specification fails to disclose that use of any and all culture conditions (i.e. culture media contents, growth factors, culture environment) would lead to the formation of an epidermal layer (as claimed) in a cultured skin construct.

Response to Arguments and Declaration

The applicant remarks and KC Faria's declaration regarding enablement issue filed on 12/20/05 has been fully considered. The applicant argues that the current enablement rejection regarding the "culture condition" is erroneous because the specification teaches one of ordinary skill in the art how to practice the claimed invention without undue experimentation. The applicant argues that the proper enablement is whether the specification teaches one ordinary skill in the art how to practice the without undue experimentation, not whether the claims themselves include those process conditions. The applicant argues that specification is enabling for practicing the claimed invention (e.g., Specification p. 7, lines 4-19, p. 9, line 1 to p. 10, line 20, p.11, line 11 to p.18, line 26, p. 19 line 7 to p. 20 line 1 19 Examples 1, 3, 5, 6,

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9, 10, 15, 17 and figure 1). Furthermore considering the Wand factor analysis the applicant concluded that the quantity of experimentation needed, if any, would not be undue. The applicant argues that one of ordinary skill in the art with the prerequisite education and work experience would know how to practice the cell culture conditions for which the state of technology is well known in the art. The applicant further argues that the specification discloses how to prepare a layer of extracellular matrix from dermal fibroblast cells in the absence of exogenous matrix components. The applicant further argues that the present specification provides working examples of culturing human fibroblasts and formation of an epidermal layer. The applicant concluded that therefore, for all of these reasons, one of ordinary skill in the art would be able to practice the claimed invention without undue experimentation especially in view of Faria's Declaration. The applicant asserts that enablement is incorrect because one ordinary skilled in the art can practice the invention as claimed without undue amount of experimentation in view of guidance provided in the specification.

The Faria's declaration asserts that one of ordinary skill in the art would understand based on instant application how to prepare without undue experimentation a cultured skin construct with at least two layers comprising cultured fibroblasts which synthesize, assemble and produce a layer of extracellular matrix in the absence of both exogenous matrix components and a mesh member during the culturing conditions, and a second layer of epidermal cells which may form an epimerized cell layer when the seeded epithelial cells are keratinocytes. The declaration further states that it is well known in the art what culture media may be used to obtain layer of fibroblast or epidermal cells. The declaration further states that it is well known in the art what culture media to use to grow a layer of dermal fibroblast or epidermal layer to produce their natural byproducts. The declaration further states that armed with the knowledge of how to practice the cell culture conditions for which the state of the technology is well known in the art, how to prepare a layer of extracellular matrix from dermal fibroblast cells in the absence of exogenous matrix components and how to grow human fibroblasts and epidermal cells, one of ordinary skill in the art would understand how to practice the

claimed invention. The declaration concluded that experimentation if any is needed would be routine at most and certainly would not be undue.

However, applicant's arguments are found not fully persuasive. The scope of "culturing conditions" as claimed is not limited to the disclosure of culture media alone but encompasses conditions under which a designated media(s) is used to make the cultured skin construct as claimed. The invention as claimed encompasses multi-layered cultured skin construct comprising a layer of cultured dermal fibroblast cells, which produce a layer of extracellular matrix in the absence of exogenous matrix components during any and all culturing conditions. As stated earlier the invention as claimed fails to recite what are the culturing conditions, for example, culture media contents, growth factors, support structure and culture environment etc that leads to the synthesis of the claimed extracellular matrix components (I and type III collagens, decorin, fibronectin, tenascin and any and all glycosaminoglycans to support the growth and proliferation of second layer of epithelial cells. Similarly the instant claims fail to recite what are the culturing conditions (culture media contents, growth factors, culture environment that leads to the formation of epidermis.

The earlier office action clearly provided the evidence that the assembly of cells into tissues is a highly orchestrated set of events that requires time scales ranging from seconds to weeks and dimensions ranging from 0.0001 to 10 cm. Coaxing cells to form tissues in a reliable manner is the quintessential engineering design problem that must be accomplished under the classical engineering constraints of reliability (see Naughton et al Science 295:1009-1014, 2002). Therefore defining culture conditions which are not limited to culture media alone but encompasses chemically defined medium and structures required for each step involved in the development of cultured skin construct which are considered essential practice the instant invention without further undue experimentation. Even though the specification discloses various chemically defined medias like growth medium, production medium, epidermalization medium, cornification medium, maintenance medium, chemically defined medium, seed medium, and other medias it is unclear which media is used at each step during the development of the cultured skin construct as claimed. Similarly the disclosure of a structure in the absence

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of a mesh member is considered essential practice the instant invention without further undue experimentation. Under the law, the disclosure "shall inform how to use, not how to find out how to use for themselves." See *In re Gardner* 475 F.2d 1389, 177 USPQ 396 (CCPA 1973). At issue, under the enablement requirement of 35 U.S.C. 1 12, first paragraph is whether, given the Wands factors, the experimentation was undue or unreasonable under the circumstances. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See *Fields v. Conover*, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). In instant case the with the identification of culture conditions eve one skill in the art would have to engage in excessive and undue experimentation to practice the invention as claimed.

Under the law Limitations appearing in the specification but not recited in the claim are not read into the claim. *In re Prater*, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-551 (CCPA 1969). See also *In re Zletz*, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989). Furthermore, claims are interpreted in light of the specification does not mean that everything in the specification must be read into the claims. *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 957, 220 USPQ 592, 597 (Fed. Cir. 1983), cert. denied, 469 U.S. 835 (1984). See also MPEP § 2111 - § 2111.01

Although a claim should be interpreted in light of the specification disclosure, it is generally considered improper to read limitations contained in the specification into the claims. See *In re Prater*, 415 F.2d 1393, 162 USPQ 541 (CCPA 1969) and *In re Winkhaus*, 527 F.2d 637, 188 USPQ 129 (CCPA 1975), *In re Van Guens*, 988 F.2d 1181, 26 PSPG2d 1057 (Ded. Cir. 1991), which discuss the premise that one cannot rely on the specification to impart limitations to the claim that are not recited in the claim. Accordingly, without the recitation of all these critical limitations, the claims do not adequately define the instant invention. Similarly in the instant case the claims fail to recite what encompasses the "chemically defined media" or "culturing conditions" as claimed. In addition if the language of the claim is such that a person of ordinary skill in the art could not interpret the metes and bounds of the claim so as to understand how to avoid infringement, a rejection of the claim under 35 U.S.C. 112, second paragraph would be appropriate. See *Morton Int 'l, Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 1470,

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28 USPQ2d 1190, 1195 (Fed. Cir. 1993). See MPEP 173.02. In instant case it is unclear how one would envision the invention as claimed to avoid infringement issues especially in context of “culturing conditions” or “chemically defined media”, especially when the process of making a cultured skin construct is multi-factorial.

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of skill. In instant case making a multi-layered cultured skin construct under any and all culture conditions (culture media contents, growth factors, culture environment etc) is not considered routine in the art and without sufficient guidance to a specific “culturing conditions” the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102/103

The prior art rejection under 35 USC 102 and 103 has been withdrawn, since Lam et al (US 6,733,530, 2004) is not a prior art under 35 USC 102(e).

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not


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mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to **571-272-0547**. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**


SUMESH KAUSHAL
PRIMARY EXAMINER
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